CLAIMS

1. (currently amended) A composition comprising:

(a) a drug in a pharmaceutically acceptable solubility-improved form; and

(b) a concentration-enhancing polymer combined with said solubility-improved form in a sufficient amount so that said composition provides, after introduction to a use environment, a maximum concentration of said drug in said use environment that is at least 1.25-fold an equilibrium concentration of said drug in said use environment, and a concentration of said drug in said use environment that exceeds said equilibrium concentration for a longer time than the concentration of said drug in said use environment provided by a control composition exceeds said equilibrium concentration, wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form,

wherein

said composition is not a dispersion;

said drug has an aqueous solubility less than about 1 mg/mL;

when said drug is basic, said solubility improved form has an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form;

said concentration-enhancing polymer is a cellulosic ionizable polymer selected from the group consisting of cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate

pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, carboxymethyl ~~eyhyl~~ ethyl cellulose and ethyl picolinic acid cellulose acetate; and

said drug and said polymer are combined as a simple physical mixture.

2. (original) The composition of claim 1 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

3. (withdrawn) The composition of claim 1 wherein said drug in said solubility-improved form is a high-energy crystalline form of said drug.

4. (withdrawn) The composition of claim 1 wherein said drug in said solubility-improved form is amorphous.

5. (withdrawn) The composition of claim 1 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solubilizing agent.

6. (withdrawn) The composition of claim 5 wherein said solubilizing agent is selected from the group consisting of surfactants, pH control agents, glycerides, partial glycerides, glyceride derivatives, polyoxyethylene and polyoxypropylene ethers and their copolymers, sorbitan esters, polyoxyethylene sorbitan esters, alkyl sulfonates, and cyclodextrins.

7. (withdrawn) The composition of claim 6 wherein said pH control agents are selected from the group consisting of buffers, organic acids, organic acid salts, organic and inorganic bases, and organic and inorganic base salts.

8. (withdrawn) The composition of claim 5 wherein said drug is basic and said solubilizer is an organic acid selected from the group consisting of adipic acid, citric acid,

fumaric acid, malic acid, succinic acid, tartaric acid, erythorbic acid, maleic acid, L-aspartic acid, L-glutamic acid, tannic acid, and D,L-tyrosine.

9. (withdrawn) The composition of claim 1 wherein said drug in said solubility-improved form is a solution of a drug substantially dissolved in a liquid to a concentration that is at least 10-fold said equilibrium concentration of said drug in said use environment.

10. (withdrawn) The composition of claim 9 wherein said liquid is selected from the group consisting of water-immiscible triglyceride vegetable oils, water-immiscible refined and synthetic and semisynthetic oils, mono-, di- and tri-glycerides, water-miscible alcohols, and water-miscible polyethyleneglycols.

11. (withdrawn) The composition of claim 9 wherein said liquid comprises water and a water-soluble solubilizer.

12. (original) The composition of claim 1 wherein said use environment is *in vivo*.

13. (original) The composition of claim 12 wherein said use environment is selected from the group consisting of the GI tract, subcutaneous space, vaginal tract, pulmonary tract, arterial and venous blood vessels, and intramuscular tissue of an animal.

14. (original) The composition of claim 1 wherein said use environment is *in vitro*.

15. (original) The composition of claim 1 wherein said concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

16. (canceled)

17. (canceled)

18. (previously presented) The composition of claim 1 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

19. (withdrawn) The composition of claim 1 wherein said polymer is a non-ionizable cellulosic polymer.

20. (withdrawn) The composition of claim 19 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose.

21. (withdrawn) The composition of claim 1 wherein said polymer is an ionizable, non-cellulosic polymer.

22. (withdrawn) The composition of claim 21 wherein said polymer is selected from the group consisting of carboxylic acid functionalized polymethacrylates, carboxylic acid functionalized polyacrylates, amine-functionalized polyacrylates, amine-fuctinoalized polymethacrylates, proteins, and carboxylic acid functionalized starches.

23. (withdrawn) The composition of claim 1 wherein said polymer is a non-ionizable, non-cellulosic polymer.

24. (withdrawn) The composition of claim 23 wherein said polymer is selected from the group consisting of polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinyl pyrrolidone, polyethylene polyvinyl alcohol copolymers, and chitin.

25. (original) The composition of claim 1 wherein said composition provides a dissolution area under the concentration versus time curve in a use environment for a period of at least 90 minutes during the 1200 minutes immediately following introduction to

said use environment that is at least 1.25-fold the corresponding area under the curve provided by said control composition.

26. (original) The composition of claim 1 wherein said maximum concentration of said drug in said use environment is at least 2-fold said equilibrium concentration.

27. (original) The composition of claim 1 wherein said composition provides a relative bioavailability of at least 1.25.

28. (original) The composition of claim 1 wherein said composition provides a maximum concentration in said use environment that is at least 1.25-fold the maximum drug concentration in said use environment provided by said control composition.

29. (original) The composition of claim 1 wherein said drug is selected from antihypertensives, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatories, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, and antiviral agents.

30. (currently amended) A composition comprising:

(a) a drug in a pharmaceutically acceptable solubility-improved form; and

(b) a concentration-enhancing polymer combined with said drug in a sufficient amount so that said composition provides, after introduction to a use environment, a dissolution area under the concentration versus time curve in said use environment for a period of at least 90 minutes during the 1200 minutes immediately following introduction to said use environment that is at least 1.25-fold the corresponding area under the curve provided by a control composition, wherein said control composition is free from said concentration-enhancing polymer and

comprises an equivalent quantity of said drug in said solubility-improved form,

wherein

said composition is not a dispersion;

said drug has an aqueous solubility less than about 1 mg/mL;

when said drug is basic, said solubility improved form has an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form;

said concentration-enhancing polymer is a cellulosic ionizable polymer selected from the group consisting of cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, carboxymethyl ~~eyhyl~~ ethyl cellulose and ethyl picolinic acid cellulose acetate; and

said drug and said polymer are combined as a simple physical mixture.

31. (original) The composition of claim 30 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

32. (withdrawn) The composition of claim 30 wherein said drug in said solubility-improved form is a high-energy crystalline form of said drug.

33. (withdrawn) The composition of claim 30 wherein said drug in said solubility-improved form is amorphous.

34. (withdrawn) The composition of claim 30 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solubilizing agent.

35. (withdrawn) The composition of claim 34 wherein said solubilizing agent is selected from the group consisting of surfactants, pH control agents, glycerides, partial glycerides, glyceride derivatives, polyoxyethylene and polyoxypropylene ethers and their copolymers, sorbitan esters, polyoxyethylene sorbitan esters, carbonate salts, alkyl sulfonates, and cyclodextrins.

36. (withdrawn) The composition of claim 35 wherein said pH control agents are selected from the group consisting of buffers, organic acids, organic acid salts, organic and inorganic bases, and organic and inorganic base salts.

37. (withdrawn) The composition of claim 34 wherein said drug is basic and said solubilizer is an organic acid selected from the group consisting of adipic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid, erythorbic acid, maleic acid, L-aspartic acid, L-glutamic acid, tannic acid, and D,L-tyrosine.

38. (withdrawn) The composition of claim 30 wherein said drug in said solubility-improved form is a solution of a drug substantially dissolved in a liquid to a concentration that is at least 10-fold said equilibrium concentration of said drug in said use environment.

39. (withdrawn) The composition of claim 38 wherein said liquid is selected from the group consisting of water-immiscible triglyceride vegetable oils, water-immiscible refined and synthetic and semisynthetic oils, mono-, di-, and tri-glycerides, water-miscible alcohols, and water-miscible polyethyleneglycols.

40. (withdrawn) The composition of claim 38 wherein said liquid comprises water and a water-soluble solubilizer.

41. (original) The composition of claim 30 wherein said use environment is *in vivo*.

42. (original) The composition of claim 41 wherein said use environment is selected from the group consisting of the GI tract, subcutaneous space, vaginal tract, pulmonary tract, arterial and venous blood vessels, and intramuscular tissue of a mammal.

43. (original) The composition of claim 30 wherein said use environment is *in vitro*.

44. (original) The composition of claim 30 wherein said concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

45. (canceled)

46. (canceled)

47. (previously presented) The composition of claim 30 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

48. (withdrawn) The composition of claim 30 wherein said polymer is a non-ionizable cellulosic polymer.

49. (withdrawn) The composition of claim 48 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose.

50. (withdrawn) The composition of claim 30 wherein said polymer is an ionizable, non-cellulosic polymer.

51. (withdrawn) The composition of claim 50 wherein said polymer is selected from the group consisting of carboxylic acid functionalized polymethacrylates, carboxylic acid functionalized polyacrylates, amine-functionalized polyacrylates, amine-fuctinoalized polymethacrylates, proteins, and carboxylic acid functionalized starches.

52. (withdrawn) The composition of claim 30 wherein said polymer is a non-ionizable, non-cellulosic polymer.

53. (withdrawn) The composition of claim 52 wherein said polymer is selected from the group consisting of polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinyl pyrrolidone, polyethylene polyvinyl alcohol copolymers, and chitin.

54. (original) The composition of claim 30 wherein said composition provides a maximum concentration of said drug in said use environment that is at least 1.25-fold said equilibrium concentration of said drug provided by said control.

55. (original) The composition of claim 30 wherein said composition provides a relative bioavailability of at least 1.25-fold.

56. (original) The composition of claim 30 wherein said drug is selected from antihypertensives, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatories, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, and antiviral agents.

57. (original) The composition of claim 30 wherein said drug concentration provided by said composition is greater than the equilibrium concentration of said drug for at least 15 minutes.

58. (currently amended) A composition comprising:

(a) a drug in a pharmaceutically acceptable solubility-improved form; and

(b) a concentration-enhancing polymer combined with said drug in a sufficient amount so that said composition provides, after introduction to a use environment, a relative bioavailability of at least 1.25 relative to a control composition that is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form,

wherein

said composition is not a dispersion;

said drug has an aqueous solubility less than about 1 mg/mL;

when said drug is basic, said solubility improved form has an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form;

said concentration-enhancing polymer is a cellulosic ionizable polymer selected from the group consisting of cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl

nicotinic acid cellulose acetate, carboxymethyl ~~eyhyl~~ ethyl cellulose and ethyl picolinic acid cellulose acetate; and

said drug and said polymer are combined as a simple physical mixture.

59. (original) The composition of claim 58 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

60. (withdrawn) The composition of claim 58 wherein said drug in said solubility-improved form is a high energy crystalline form of said drug.

61. (withdrawn) The composition of claim 58 wherein said drug in said solubility-improved form is amorphous.

62. (withdrawn) The composition of claim 58 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solubilizing agent.

63. (withdrawn) The composition of claim 62 wherein said solubilizing agent is selected from the group consisting of surfactants, pH control agents, glycerides, partial glycerides, glyceride derivatives, polyoxyethylene and polyoxypropylene ethers and their copolymers, sorbitan esters, polyoxyethylene sorbitan esters, carbonate salts, alkyl sulfonates, and cyclodextrins.

64. (withdrawn) The composition of claim 63 wherein said pH control agents are selected from the group consisting of buffers, organic acids, organic acid salts, organic and inorganic bases, and organic and inorganic base salts.

65. (withdrawn) The composition of claim 62 wherein said drug is basic and said solubilizer is an organic acid selected from the group consisting of adipic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid, erythorbic acid, maleic acid, L-aspartic acid, L-glutamic acid, tannic acid, and D,L-tyrosine.

66. (withdrawn) The composition of claim 58 wherein said drug in said solubility-improved form is a solution of a drug substantially dissolved in a liquid to a concentration that is at least 10-fold said equilibrium concentration of said drug in said use environment.

67. (withdrawn) The composition of claim 66 wherein said liquid is selected from the group consisting of water-immiscible triglyceride vegetable oils, water-immiscible refined and synthetic and semisynthetic oils, mono-, di-, and tri-glycerides, water-miscible alcohols, and water-miscible polyethyleneglycols.

68. (withdrawn) The composition of claim 66 wherein said liquid comprises water and a water-soluble solubilizer.

69. (original) The composition of claim 58 wherein said use environment is *in vivo*.

70. (original) The composition of claim 88 wherein said use environment is selected from the group consisting of the GI tract, subcutaneous space, vaginal tract, pulmonary tract, arterial and venous blood vessels, and intramuscular tissue of an animal.

71. (original) The composition of claim 58 wherein said use environment is *in vitro*.

72. (original) The composition of claim 58 wherein said concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

73. (canceled)

74. (canceled)

75. (previously presented) The composition of claim 58 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate

succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

76. (withdrawn) The composition of claim 58 wherein said polymer is a non-ionizable cellulosic polymer.

77. (withdrawn) The composition of claim 76 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose.

78. (withdrawn) The composition of claim 58 wherein said polymer is an ionizable, non-cellulosic polymer.

79. (withdrawn) The composition of claim 78 wherein said polymer is selected from the group consisting of carboxylic acid functionalized polymethacrylates, carboxylic acid functionalized polyacrylates, amine-functionalized polyacrylates, amine-fuctinoalized polymethacrylates, proteins, and carboxylic acid functionalized starches.

80. (withdrawn) The composition of claim 58 wherein said polymer is a non-ionizable, non-cellulosic polymer.

81. (withdrawn) The composition of claim 80 wherein said polymer is selected from the group consisting of polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinyl pyrrolidone, polyethylene polyvinyl alcohol copolymers, and chitin.

82. (original) The composition of claim 58 wherein said composition provides a maximum concentration of said drug in said use environment that is at least 1.25-fold said equilibrium concentration of said drug provided by said control.

83. (original) The composition of claim 58 wherein said composition provides a maximum concentration of said drug in said use environment that is at least 2-fold said equilibrium concentration.

84. (original) The composition of claim 58 wherein said drug is selected from antihypertensives, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatories, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, and antiviral agents.

85. (original) The composition of claim 58 wherein said drug concentration provided by said composition exceeds the equilibrium concentration of said drug for at least 15 minutes.

86. (currently amended) A method of administering a drug comprising co-administering to a patient in need of said drug:

(a) a drug in a solubility-improved form; and

(b) a concentration-enhancing polymer;

wherein

said concentration-enhancing polymer is co-administered with said solubility-improved form in a sufficient amount, so that after introduction to a use environment, a maximum concentration of said drug in said use environment is provided that is at least 1.25-fold an equilibrium concentration of said drug in said use environment provided by a control composition;

a concentration of said drug in said use environment is provided that exceeds said equilibrium concentration for a longer time than the concentration of said drug in said use environment provided by said control composition exceeds said equilibrium concentration;

said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form,

(a) and (b) are not administered in a dispersion;

said drug has an aqueous solubility less than about 1 mg/mL;

when said drug is basic, said solubility improved form has an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form;

said concentration-enhancing polymer is a cellulosic ionizable polymer selected from the group consisting of cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, carboxymethyl ~~eyhyl~~ ethyl cellulose and ethyl picolinic acid cellulose acetate; and

said drug and said polymer are combined as a simple physical mixture.

87. (original) The method of claim 86 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

88. (withdrawn) The method of claim 86 wherein said drug in said solubility-improved form is a high-energy crystalline form of said drug.

89. (withdrawn) The method of claim 86 wherein said drug in said solubility-improved form is amorphous.

90. (withdrawn) The method of claim 86 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solubilizing agent.

91. (withdrawn) The method of claim 86 wherein said drug in said solubility-improved form is a solution of a drug substantially dissolved in a liquid to a concentration that is at least 10-fold an equilibrium concentration of said drug in said use environment.

92. (original) The method of claim 86 wherein said concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

93. (canceled)

94. (canceled)

95. (previously presented) The method of claim 86 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

96. (withdrawn) The method of claim 86 wherein said polymer is a non-ionizable cellulosic polymer.

97. (withdrawn) The method of claim 96 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose.

98. (withdrawn) The method of claim 86 wherein said polymer is an ionizable, non-cellulosic polymer.

99. (withdrawn) The method of claim 98 wherein said polymer is selected from the group consisting of carboxylic acid functionalized polymethacrylates, carboxylic acid functionalized polyacrylates, amine-functionalized polyacrylates, amine-fuctinoalized polymethacrylates, proteins, and carboxylic acid functionalized starches.

100. (withdrawn) The method of claim 86 wherein said polymer is a non-ionizable, non-cellulosic polymer.

101. (withdrawn) The method of claim 100 wherein said polymer is selected from the group consisting of polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinyl pyrrolidone, polyethylene polyvinyl alcohol copolymers, and chitin.

102. (original) The method of claim 86 wherein a maximum concentration in said use environment is provided that is at least 1.25-fold the maximum drug concentration in said use environment provided by said control composition.

103. (canceled)

104. (previously presented) The method of claim 86 wherein said drug and said concentration-enhancing polymer are administered at essentially the same time.

105. (original) The method of claim 86 wherein said drug is administered in a composition also comprising said concentration-enhancing polymer.

106. (currently amended) A method of administering a drug comprising co-administering to a patient in need of said drug:

(a) a drug in a solubility-improved form; and

(b) a concentration-enhancing polymer;

wherein

said concentration-enhancing polymer is co-administered with said drug in a sufficient amount so that, after introduction to a use environment, a dissolution area under the concentration versus time curve is provided in said use environment for a period of at least 90 minutes during the 1200 minutes immediately following introduction to said use environment that is at least 1.25-fold the corresponding area under the curve provided by a control composition;

said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form,

(a) and (b) are not administered in a dispersion;

said drug has an aqueous solubility less than about 1 mg/mL;

when said drug is basic, said solubility improved form has an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form;

said concentration-enhancing polymer is a cellulosic ionizable polymer selected from the group consisting of cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, carboxymethyl ethyl cellulose and ethyl picolinic acid cellulose acetate; and

said drug and said polymer are combined as a simple physical mixture.

107. (original) The method of claim 106 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

108. (withdrawn) The method of claim 106 wherein said drug in said solubility-improved form is a high-energy crystalline form of said drug.

109. (withdrawn) The method of claim 106 wherein said drug in said solubility-improved form is amorphous.

110. (withdrawn) The method of claim 106 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solubilizing agent.

111. (withdrawn) The method of claim 106 wherein said drug in said solubility-improved form is a solution of a drug substantially dissolved in a liquid to a concentration that is at least 10-fold an equilibrium concentration of said drug in said use environment.

112. (original) The method of claim 106 wherein said concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

113. (canceled)

114. (canceled)

115. (previously presented) The method of claim 106 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

116. (withdrawn) The method of claim 106 wherein said polymer is a non-ionizable cellulosic polymer.

117. (withdrawn) The method of claim 106 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose.

118. (withdrawn) The method of claim 106 wherein said polymer is an ionizable, non-cellulosic polymer.

119. (withdrawn) The method of claim 118 wherein said polymer is selected from the group consisting of carboxylic acid functionalized polymethacrylates, carboxylic acid functionalized polyacrylates, amine-functionalized polyacrylates, amine-fuctinoalized polymethacrylates, proteins, and carboxylic acid functionalized starches.

120. (withdrawn) The method of claim 106 wherein said polymer is a non-ionizable, non-cellulosic polymer.

121. (withdrawn) The method of claim 120 wherein said polymer is selected from the group consisting of polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinyl pyrrolidone, polyethylene polyvinyl alcohol copolymers, and chitin.

122. (original) The method of claim 106 wherein a maximum concentration in said use environment is provided that is at least 1.25-fold the maximum drug concentration in said use environment provided by said control composition.

123. (canceled)

124. (previously presented) The method of claim 106 wherein said drug and said concentration-enhancing polymer are administered at essentially the same time.

125. (original) The method of claim 106 wherein said drug is administered in a composition also comprising said concentration-enhancing polymer.

126. (currently amended) A method of administering a drug comprising co-administering to a patient in need of said drug:

(a) a drug in a solubility-improved form; and

(b) a concentration-enhancing polymer;

wherein

said concentration-enhancing polymer is co-administered with said drug in a sufficient amount so that, after introduction to a use environment, a relative bioavailability is

provided of at least 1.25-fold that of a control composition, wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form,

(a) and (b) are not administered in a dispersion;

said drug has an aqueous solubility less than about 1 mg/mL;

when said drug is basic, said solubility improved form has an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form;

said concentration-enhancing polymer is a cellulosic ionizable polymer selected from the group consisting of cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, carboxymethyl ethyl cellulose and ethyl picolinic acid cellulose acetate; and

said drug and said polymer are combined as a simple physical mixture.

127. (original) The method of claim 126 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

128. (withdrawn) The method of claim 126 wherein said drug in said solubility-improved form is a high-energy crystalline form of said drug.

129. (withdrawn) The method of claim 126 wherein said drug in said solubility-improved form is amorphous.

130. (withdrawn) The method of claim 126 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solubilizing agent.

131. (withdrawn) The method of claim 126 wherein said drug in said solubility-improved form is a solution of a drug substantially dissolved in a liquid to a concentration that is at least 10-fold an equilibrium concentration of said drug in said use environment.

132. (original) The method of claim 126 wherein said concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

133. (canceled)

134. (canceled)

135. (previously presented) The method of claim 126 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

136. (withdrawn) The method of claim 126 wherein said polymer is a non-ionizable cellulosic polymer.

137. (withdrawn) The method of claim 126 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose.

138. (withdrawn) The method of claim 126 wherein said polymer is an ionizable, non-cellulosic polymer.

139. (withdrawn) The method of claim 138 wherein said polymer is selected from the group consisting of carboxylic acid functionalized polymethacrylates, carboxylic acid functionalized polyacrylates, amine-functionalized polyacrylates, amine-fuctinoalized polymethacrylates, proteins, and carboxylic acid functionalized starches.

140. (withdrawn) The method of claim 126 wherein said polymer is a non-ionizable, non-cellulosic polymer.

141. (withdrawn) The method of claim 140 wherein said polymer is selected from the group consisting of polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinyl pyrrolidone, polyethylene polyvinyl alcohol copolymers, and chitin.

142. (original) The method of claim 126 wherein a maximum concentration in said use environment is provided that is at least 1.25-fold the maximum drug concentration in said use environment provided by said control composition.

143. (original) The method of claim 126 wherein said drug is administered separately from said concentration-enhancing polymer.

144. (original) The method of claim 143 wherein said drug and said concentration-enhancing polymer are administered at essentially the same time.

145. (original) The method of claim 126 wherein said drug is administered in a composition also comprising said concentration-enhancing polymer.

146. (original) An aqueous solution formed by administration of a solid drug in a solubility-improved form and a concentration-enhancing polymer to a use environment, comprising:

(a) each of said drug and said concentration-enhancing polymer being at least partially dissolved in said solution;

(b) at least a portion of said dissolved drug being associated with at least a portion of said polymer in a plurality of assemblies of drug and polymer, said assemblies having a size of from about 10 to 1000 nanometers; and

(c) said solution having a maximum concentration of said drug that is at least 1.25-fold an equilibrium concentration of said drug in said use environment, and a concentration of said drug that exceeds said equilibrium concentration for a longer time than the concentration of said drug in said use environment provided by a control composition exceeds said equilibrium concentration, wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form.

147. (original) The solution of claim 146 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

148. (withdrawn) The solution of claim 146 wherein said drug in said solubility-improved form is a high-energy crystalline form of said drug.

149. (withdrawn) The solution of claim 146 wherein said drug in said solubility-improved form is amorphous.

150. (withdrawn) The solution of claim 146 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solid solubilizing agent.

151. (original) The solution of claim 146 wherein said use environment is *in vivo*.

152. (original) The solution of claim 146 wherein said use environment is selected from the group consisting of the GI tract, subcutaneous space, vaginal tract, pulmonary tract, arterial and venous blood vessels, and intramuscular tissue of an animal.

153. (original) The solution of claim 146 wherein said use environment is *in vitro*.

154. (original) The solution of claim 146 wherein said concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

155. (original) An aqueous solution formed by administration of a drug in a solubility-improved form and a concentration-enhancing polymer to a use environment, comprising:

(a) each of said drug and said concentration-enhancing polymer being at least partially dissolved in said solution;

(b) at least a portion of said dissolved drug being associated with at least a portion of said polymer in a plurality of assemblies of drug and polymer, said assemblies having a size of from about 10 to 1000 nanometers;

(c) said polymer being selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate trimellitate, cellulose acetate terephthalate and cellulose acetate isophthalate; and

(d) said solution having a maximum concentration of said drug that is at least 1.25-fold an equilibrium concentration of said drug in said use environment, and a concentration of said drug that exceeds said equilibrium concentration for a longer time than the concentration of said drug in said use environment provided by a control composition exceeds said equilibrium concentration, wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form.

156. (previously added) The composition of claim 1, wherein said drug is ziprasidone.

157. (previously added) The composition of claim 30, wherein said drug is ziprasidone.

158. (previously added) The composition of claim 58, wherein said drug is ziprasidone.

159. (previously added) The method of claim 86, wherein said drug is ziprasidone.

160. (previously added) The method of claim 106, wherein said drug is ziprasidone.

161. (previously added) The method of claim 126, wherein said drug is ziprasidone.

162. (previously added) The solution of claim 146, wherein said drug is ziprasidone.

163. (previously added) The solution of claim 155, wherein said drug is ziprasidone.

Pharmaceutical Sciences 1995, 1: 255–258
Received April 19, 1995
Accepted May 31, 1995

Dissolution Behaviour of Efonidipine Hydrochloride

TOSHIO OKABE, TOMOKO INOUE, YOUSUKE MIYAMOTO, MASAHARU MIYAJIMA, HIROSHI SATO, MASAHIRO TAKAHASHI*, KIYOTOMO SETO*, MAKOTO OTSUKA† AND YOSHIHISA MATSUDA†

*Department of Pharmaceutics, Central Research Laboratories, Zeria Pharmaceutical Co., Ltd, 2512–1 Oshikiri, Konan-machi, Osato-gun, Saitama, 360–01, *Central Research Institute, Nissan Chemical Industries, Ltd, 722–1 Tsuboi-cho, Funabashi-shi, Chiba, 274, and †Department of Pharmaceutical Technology, Kobe Pharmaceutical University, Motoyama-Kitamachi 4–19–1, Higashi-Nada, Kobe 658, Japan*

Abstract

The dissolution behaviour of efonidipine hydrochloride, a highly potent and sustained anti-hypertensive agent, was compared with that of efonidipine.

Using the powder dispersion method, concentrations of efonidipine in solutions of pH 1·2 and pH 6·8 containing minor amounts of surfactant came to a constant value (1·7 and 1·8 $\mu g\,mL^{-1}$ at pH 1·2 and 6·8, respectively) after 2 h, indicating the equilibrium solubility of efonidipine. Characteristic convex dissolution curves with maximum values of 42·8 and 31·2 $\mu g\,mL^{-1}$ in solutions of pH 1·2 and pH 6·8, respectively, at 3 h were obtained in the dissolution of hydrochloride, in which concentrations of hydrochloride decreased to close to the solubility of efonidipine at 24 h.

This phenomenon appeared to be due to the transformation of hydrochloride to less-soluble efonidipine caused by the release of hydrochloride and ethanol during the dissolution process. Using the constant surface area method, the intrinsic solubility of hydrochloride estimated from the dissolution curve was 40·8 $\mu g\,mL^{-1}$ and the transfer rate constant from hydrochloride to efonidipine, which has a different crystalline state, was $6{\cdot}75 \times 10^{-3}\ min^{-1}$.

Drugs with solubility of less than 1 $mg\,mL^{-1}$ in the physiologic pH range 1–7 have potential problems of bioavailability, and therefore improving the dissolution of the drug from the dosage form is of importance in preformulation and formulation studies. Many attempts have been made to improve dissolution by changing crystalline form, particle size, and chemical modification. Salt forms, which have relatively high solubility and quick dissolution compared with original forms, have often been utilized by pharmaceutical chemists due to the low cost of raw materials, ease of recrystallization and high yield. Hydrochloride is the most frequently used salt (Ravin 1980). Efonidipine was developed by Nissan Chemical Co., Ltd for the treatment of high blood pressure, and its solubility range was found to be far less than 1 $mg\,mL^{-1}$ in the physiologic pH range. Efonidipine hydrochloride was synthesized to improve this poor solubility. However, the maximum solubility of the hydrochloride was observed to be remarkably higher than that of efonidipine. Although this kind of phenomenon has been reported in the case of the sulphamonomethoxine/18-crown-6 complex (Takayama et al 1978 a, b), crystalline solvated (Shefter & Higuchi 1963; Otsuka et al 1990, 1992), and polymorph (Nogami et al 1967; Higuchi et al 1967; Miyazaki et al 1974; Ueda et al 1984), there has been no study on drugs with hydrochlorides.

In this paper, the dissolution mechanism and intrinsic solubility of hydrochloride are discussed.

Correspondence: M. Miyajima, Department of Pharmaceutics, Central Research Laboratories, Zeria Pharmaceutical Co., Ltd, 2512–1 Oshikiri, Konan-machi, Osato-gun, Saitama 360-01, Japan.

Materials and Methods

Materials

Efonidipine hydrochloride (Lot No. 110P8604) and efonidipine base (Lot No. YK14009) were provided by Nissan Chemical Industries, Ltd. The hydrochloride (Fig. 1) is a salt form prepared by adding hydrochloride and ethanol to efonidipine. Polysorbate-80 (Nikkol TO-10M) and membrane filter (0·2 mm, cellulose acetate) were supplied by Nikko Chemicals Co. and Toyo Roshi Kaisha, Ltd., respectively. Hydrochloric acid and sodium chloride used were of reagent grade.

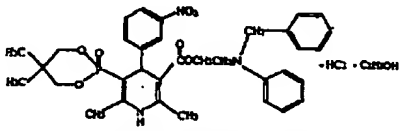


FIG. 1. Structural formula of efonidipine hydrochloride.

Powder X-ray diffraction analysis

X-ray diffraction patterns were obtained at room temperature using an X-ray diffractometer (RAD-B, Rigaku Denki). The operational conditions were as follows: radiation, Cu-K(α); filter, Ni; voltage, 40kV; current, 20 mA; receiving slit, 0·15 mm; scanning speed, 2° min^{-1}.

Infrared (IR) spectrometry

IR spectra were measured using an IR700 spectrophotometer (Japan Spectroscopic Co., Ltd) with a KBr

disk of 10 mm diameter compressed by a hydraulic press under 400 kgf cm^{-2}.

Elemental analysis
Elemental analysis was performed for C, H and N with a CHN coder (model 2400, Perkin-Elmer Japan Co.).

Thermal analysis
Thermogravimetry (TG) was performed using a model 2000 TG-DTA instrument (Mac Science Co.). In addition, differential scanning calorimetry (DSC) (model 3100, Mac Science Co.) was performed using an aluminum sample cell. The following operational conditions were employed: sample volume, 5 mg; heating rate, 10°C min^{-1}; N, gas flow rate, 30 mL min^{-1}.

Dissolution studies
Powder dispersion method. According to the paddle method described in the Japanese Pharmacopoeia XII (JP XII), 50 mg efonidipine (or hydrochloride) was introduced into 500 mL of the solution at pH 1·2 or 6·8 containing 0·05% polysorbate-80 maintained at 37±0·5°C under 150 rev min^{-1} paddle rotation speed. The particle size of efonidipine (and hydrochloride) used in the studies was less than 150 μm. Five millilitres of the solution was withdrawn with a syringe at pre-fixed intervals and filtered immediately through a membrane filter. The volume of the solution in the dissolution vessel was maintained at 500 mL by making up for loss with additional dissolution solution at 37±0·5°C. Concentration of the drug dissolved was determined by UV-spectrophotometry (UV-240, Shimadzu Co.) at 330 nm. After 24 h, undissolved material in the solution was collected for further investigation and dried in a desiccator after rinsing with distilled water.

Dissolution behaviour using the constant surface area method (Nogami et al 1966). In this study, a pellet consisting of 100 mg efonidipine, efonidipine hydrochloride or undissolved material was prepared by a single-punch tableting machine with a 1-cm^2 flat-faced punch at 2·0 ton cm^{-2} and fixed in the holder to give a constant surface area over the course of the experiment in dissolution solution. The dissolution solution (50 mL) used in this study was the same as that used in the powder dispersion method at pH 1·2. The pellet fixed to the holder was positioned 3 cm above the magnetic stirrer bar agitated at 20 rev min^{-1}. Dissolution was monitored continuously using a flow-type cell.

Results and Discussion

Dissolution behaviour of efonidipine and hydrochloride
The dissolution curves of efonidipine and hydrochloride in the solutions of pH 1·2 and 6·8 are shown in Fig. 2. In both solutions, the concentration of efonidipine in the solution increased gradually to give constant values of 1·7 and 1·8 μg mL^{-1} after 2 h in the solutions of pH 1·2 and pH 6·8, respectively, indicating the solubility of efonidipine. Concentrations of hydrochloride increased rapidly to give maximum concentrations of 42·8 and 31·2 μg mL^{-1} in the solutions of pH 1·2 and 6·8, respectively, at about 3 h, and then declined to about 4·1 μg mL^{-1} after 24 h. The maximum

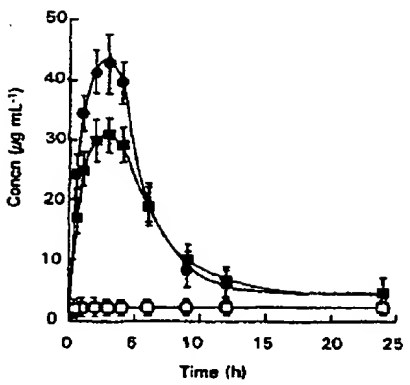


FIG. 2. Dissolution profiles of efonidipine and efonidipine hydrochloride in the solution of pH 1·2 and 6·8 by the powder dispersion method. ○ Efonidipine in pH 1·2; □ efonidipine in pH 6·8; ● efonidipine hydrochloride in pH 1·2; ■ efonidipine hydrochloride in pH 6·8. Vertical bars show mean value ± s.e.m. (n = 3).

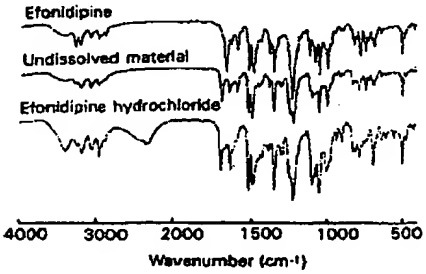


FIG. 3. Infrared absorption spectra of efonidipine, efonidipine hydrochloride and undissolved material.

concentration observed was about 25 times that in pH 1·2 and about 17 times that at pH 6·8 compared with the solubility of efonidipine. However, the concentration of hydrochloride after 24 h was only twice that of efonidipine. This type of dissolution curve was not observed with nicardipine hydrochloride categorized as a 1,4-dihydropyridine hydrochloride. Since the UV spectrum of the dissolution solution of hydrochloride collected at 24 h showed the same pattern as that of efonidipine, efonidipine hydrochloride in the solution was considered to be converted to efonidipine by the release of hydrochloride and ethanol. To evaluate this hypothesis, instrumental analysis including IR spectrometry, elementary analysis, thermal analysis and X-ray diffraction analysis was performed with three materials (efonidipine, efonidipine hydrochloride and undissolved material). The IR spectrum of the hydrochloride (Fig. 3) had a characteristic peak attributable to NH^+(quadoricate) at 2300–2800 cm^{-1}, but no peak at that range was observed in efonidipine or the undissolved material. Furthermore, peaks in the range of

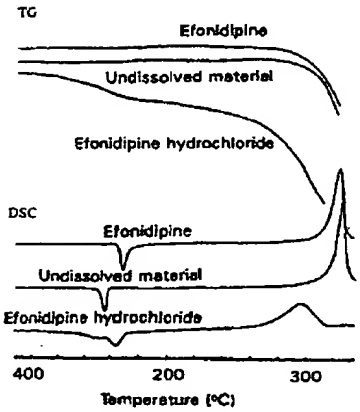


FIG. 4. DSC and TG thermograms of efonidipine, efonidipine hydrochloride and undissolved material.

1600–1700 cm^{-1} in the hydrochloride were also different from those in the other materials. The IR spectrum of efonidipine agreed well with that of undissolved material. These results suggest that the undissolved material obtained after dissolution of the hydrochloride had the same chemical formula as efonidipine. Found values for C, H and N obtained for efonidipine and undissolved material were in good agreement with theoretical values calculated on the basis of expected chemical formulae (Table 1). In the TG spectrum of the hydrochloride (Fig. 4), weight loss was observed in the range of 120–170°C, attributable to the release of hydrochloride and ethanol, but no weight loss was observed in efonidipine and undissolved material in that range. Further, the DSC pattern of hydrochloride, showing characteristic endothermic peaks at 152·4 and 164·8°C, was clearly different from that of efonidipine and undissolved material, which gave single endothermic peaks at 169·7 and 151·3°C, respectively. In powder X-ray diffraction analysis (Fig. 5), efonidipine gave characteristic diffraction peaks at 8·9, 12·2, and 17·2°, and a strong diffraction peak at 6·0° was obtained for the hydrochloride. On the other hand, the diffraction pattern of undissolved material, in which strong diffraction peaks were observed at 6·5, 7·7, 11·8, 18·3 and 20·7°, was found to be distinct from those of efonidipine and the hydrochloride. These results indicated that the three materials would have different crystalline states.

Table 1. Elemental analysis data of efonidipine, efonidipine hydrochloride and undissolved material.

Material	% Calcd (found)		
	C	H	N
Efonidipine	64·65 (64·65)	5·06 (6·19)	6·65 (6·43)
Efonidipine hydrochloride	60·54 (60·39)	5·35 (5·68)	5·88 (5·70)
Undissolved material	(64·55)	(6·29)	(6·45)

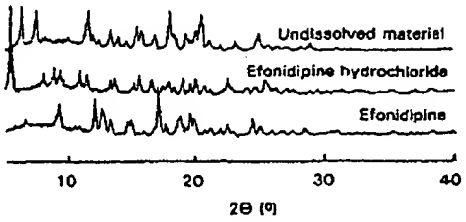


FIG. 5. X-ray diffraction patterns of efonidipine, efonidipine hydrochloride and undissolved material.

We conclude that the hydrochloride dissolved from the surface of the hydrochloride powder and changed rapidly to less-soluble efonidipine in the dissolution process by the release of hydrochloride and ethanol, and the maximum solubility may be caused by the high intrinsic solubility of hydrochloride and a balance between the dissolution rate and transformation rate from hydrochloride to efonidipine. This is consistent with the observation that the efonidipine obtained after dissolution of the hydrochloride has a different crystalline state from the efonidipine used in the present study.

Kinetic considerations

To investigate the observed phenomenon quantitatively, the dissolution behaviour of hydrochloride, efonidipine and undissolved material was examined using the constant surface area method. Kanke & Sekiguchi (1973) derived equation 1 to estimate the intrinsic solubility of the metastable form of sulphathiazole polymorphs from the Noyes-Whitney-Nernst equation:

$$C_s^* = C_s \cdot (dE^*/dt)/(dE/dt) \quad (1)$$

where C_s^* and C_s are the solubility of metastable and stable form, respectively. dE^*/dt and dE/dt are initial dissolution rates of the two forms calculated from the slope of the dissolution curve in the initial stage. However, it is difficult to estimate the initial dissolution rate quantitatively because the intrinsic solubility of the metastable form appeared at too early a stage. Accordingly, equation 2, derived by Nogami et al (1969), was used to obtain the rate constant (k_t) of the transformation to less-soluble form and intrinsic solubility (C_s^*) of hydrochloride in this study.

$$C = k_t \cdot (C_s^* - C_s)/(k_t - k_s)\{e^{-k_s t} - e^{-k_t t}\} + C_s \cdot (1 - e^{-k_t t}) \quad (2)$$

In equation 2, the apparent dissolution rate constant k_t of efonidipine was calculated using equation 3, in which dE/dt was obtained as the slope of the dissolution curve of efonidipine in the initial stage (Fig. 5), and further, C_s was estimated using the powder dispersion method (Fig. 2):

$$k_t = (dE/dt)/C_s \quad (3)$$

The dissolution behaviour of the hydrochloride was quantitatively investigated only at pH 1·2.

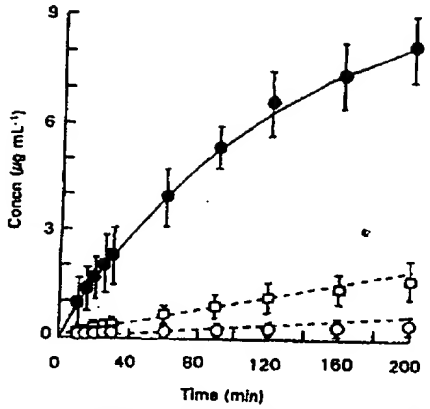


FIG. 6. Initial dissolution curves of efonidipine (○), efonidipine hydrochloride (●) and undissolved material (□) at pH 1·2 using the constant surface area method. The solid lines represent the theoretical dissolution curve. The dotted line was used to estimate an apparent dissolution rate constant (k_r) of efonidipine and undissolved material. Vertical bars show mean value ± s.e.m. ($n=3$).

C_s calculated as 4·1 μg mL^{-1} from Fig. 2 was inserted into equation 3, giving k_r as 0·00216 min^{-1}. Then, from the curve-fitting of equation 2 on dissolution data of the hydrochloride shown in Fig. 6 using the nonlinear least-square method (Yamaoka et al 1981), C_s^* and k_r were obtained as 40·8 μg mL^{-1} and $6{\cdot}75 \times 10^{-3}$ min^{-1}, respectively. Intrinsic solubility of hydrochloride was about 10 times that of the undissolved material. The dissolution curve obtained by curve-fitting is depicted in Fig. 6. Agreement between the data and the curve is reasonably good.

Dissolution behaviour of efonidipine using the constant surface area method is also shown in Fig. 6, which indicates that the k_r value of efonidipine was 0·000909 min^{-1} and its solubility less than one-twentieth that of the hydrochloride.

Conclusion

From the perspective of bioavailability, poor dissolution is a serious problem in the design of drug formulations. The conversion of free base to its hydrochloric salt is an effective method of improving this unfavourable property, but we found the equilibrium solubility of hydrochloride to be almost the same as that of efonidipine. We attribute this to the transformation of the hydrochloride, which has a high intrinsic solubility, to efonidipine in the dissolution medium. Consequently, improvement in bioavailability cannot be expected by the conversion of free base to its hydrochloric salt.

References

Higuchi, W. I., Bernardo, P. D., Methe, S. C. (1967) Polymorphism and drug availability II. Dissolution rate behavior of polymorphic forms of sulfathiazole and methylprednisolone. J. Pharm. Sci. 56: 200–207

Kanke, M., Sekiguchi, K. (1973) Dissolution behavior of solid drugs. II. Determination of the transition temperature of sulfathiazole polymorphs by measuring the initial dissolution rates. Chem. Pharm. Bull. 21: 878–884

Miyazaki, S., Arita, T., Hori, R., Ito, K. (1974) Effect of polymorphism on the dissolution behavior and gastrointestinal absorption of chlortetracycline hydrochloride. Chem. Pharm. Bull. 22: 638–647

Nogami, H., Nagai, T., Suzuki, A. (1966) Studies on powdered preparations XVII. Dissolution rate of sulfonamides by rotating disk method. Chem. Pharm. Bull. 14: 329–338

Nogami, H., Nagai, T., Fukuoka, E., Yotsuyanagi, T. (1967) Dissolution kinetics of barbital polymorphs. Chem. Pharm. Bull. 17: 23–31

Nogami, H., Nagai, T., Yotsuyanagi, T. (1969) Dissolution phenomena of organic medicinals involving simultaneous phase changes. Chem. Pharm. Bull. 17: 499–509

Otsuka, M., Teraoka, R., Matsuda, Y. (1990) Characterization of nitrofurantoin anhydrate and monohydrate, and their dissolution behaviors. Chem. Pharm. Bull. 38: 833–835

Otsuka, M., Teraoka, R., Matsuda, Y. (1992) Rotating-disk dissolution kinetics of nitrofurantoin anhydrate and monohydrate at various temperatures. Pharm. Res. 9: 303–307

Ravin, L. J. (1980) Preformulation. In: Osol, A., Chase, G. D., Gennaro, A. R., Gibson, M. R., Granberg, C. B., Zink, G. L., Harvey, S. C., King, R. E., Martin, A. N., Swinyard, E. A. (eds) Remington's Pharmaceutical Sciences. Easton, Pennsylvania

Shefter, E., Higuchi, T. (1963) Dissolution behavior of crystalline solvated and nonsolvated forms of some pharmaceutics. J. Pharm. Sci. 52: 781–791

Takayama, T., Hasegawa, S., Sasagawa, S., Nambu, N., Nagai, T. (1978a) Dissolution profile and bioavailability of sulfamonomethoxine/18-crown-6 complex in composition with sulfamonomethoxine anhydrate and hydrate. Chem. Pharm. Bull. 26: 96–100

Takayama, K., Nambu, N., Nagai, T. (1978b) Dissolution kinetics of complexes of sulfamethoxazole and sulfamonomethoxine with 18-crown-6. Chem. Pharm. Bull. 26: 2965–2970

Ueda, H., Namubu, N., Nagai, T. (1984) Dissolution behavior of chlorpropamide polymorphs. Chem. Pharm. Bull. 32: 244–250

Yamaoka, T., Tanigawara, Y., Nakagawa, T., Uno, T. (1981) Pharmacokinetic analysis program (MULTI) for microcomputer. J. Pharmacobiodyn. 4: 879–885

[redacted]

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

THIRTEENTH EDITION

Editorial Staff

Maryadele J. O'Neil, *Senior Editor*
Ann Smith, *Senior Associate Editor*
Patricia E. Heckelman, *Associate Editor*

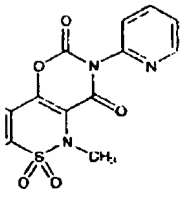
John R. Obenchain Jr., *Editorial Assistant*
Jo Ann R. Gallipeau, *Technical Assistant*
Mary Ann D'Arecca, *Administrative Associate*

Susan Budavari, *Editor Emeritus*

Published by
Merck Research Laboratories
Division of

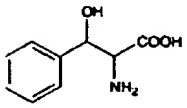
MERCK & CO., INC.
Whitehouse Station, NJ

2001



flammatory.

[23651-95-8] *threo*-β,3-Dihydroxy-4
-dihydroxyphenyl)serine; (−)-(2*S*,3*R*)-
3,4-dihydroxyphenyl)propionic acid
ro-DOPS; L-DOPS; SM-5688; Dops
.19. C 50.70%, H 5.20%, N 6.57%,
o acid precursor of norepinephrine.
W. Rosenmund, H. Domsaft, *Ber.*
n and resolution of diastereomers:
him. Acta **58**, 147 (1975); B. Hegedüs
8 (1975 to Hoffmann-La Roche).
luction: N. Ohashi *et al.*, US 4315
harmacology of stereoisomers: G.
ol. Exp. Ther. **193**, 523 (1975). Clinical
α-form and clinical evaluation in fami
athy (FAP): T. Suzuki *et al.*, *Eur.*
29 (1980). Reversed-phase chromatog
a and urine: F. Boomsma *et al.*, *J. Chr*
. Pharmacokinetics in FAP: T. Suzuki
macol. **23**, 463 (1982); in parkinsonism
logy **34**, 1446 (1984). Metabolism
uki *et al.*, *Life Sci.* **36**, 435 (1985). Cli
's disease: N. Ogawa *et al.*, *J. Med.*
ayashi *et al.*, *Advan. Neurol.* **45**,



l and ether, mp 232-235° (dec).
HCl). Also cited as crystals from
229-232° (dec) (Ohashi). $[\alpha]_D^{20}$ −

rkinsonian.

68-57-4] Delta sleep-inducing p
otide; delta sleep factor. $C_{35}H_{38}N_8O_{15}$
3%, H 5.70%, N 16.50%, O 28.27%.
s enhancement and induction of
c EEG patterns. Its occurrence was
f cerebral venous blood of rabbits
rical stimulation of the thalamus
ience **146**, 796 (1964). Initial
282, 60 (1965). Isoln, characteriza
t al., Experientia **28**, 919 (1972).
is of DSIP and analogs: G. A. Sch
r, *Proc. Nat. Acad. Sci. USA* **74**,
ynthesis: Y. P. Shvachkin *et al.*
(1981), *C.A.* **95**, 43644s (1981).
S. Nozaki, I. Murmatsu, *Bull.*
982). HPLC separation: M. Dizard
37, 417 (1982). Effect on human
t al., Lancet **I**, 1256 (1981); *idem*
r. Toxicol. **19**, 341 (1981); D. Schne
enberger, *Experientia* **37**, 913 (1981)

ily–Gly–Asp–Ala–Ser–Gly–Glu

3494. DTBP. [110-05-4] Bis(1,1-Dimethylethyl) peroxide; di-*tert*-butyl peroxide. $C_8H_{18}O_2$; mol wt 146.23. C 65.71%, H 12.41%, O 21.88%. $(CH_3)_3COOC(CH_3)_3$.

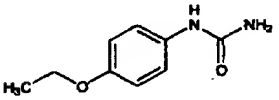
Flammable liq; d_4^{20} 0.7940; mp −40°; bp_{284} 80°; n_D^{20} 1.3890. Flash pt (Tag open cup) 65°F (18°C). Soluble in organic solvents, in most resin monomers and in partial polymers. Soly in water about 0.01%.

USE: As polymerization catalyst.

3495. Dubnium. [53850-35-4] Element 105; hahnium; nielsbohrium; unnilpentium. Db, Ha, Ns, Unp; at. no. 105. Group VB(5). No stable nuclides. Prepn of α-emitting ^{260}105 isotope ($T_{1/2}$ 1.6±0.3 sec) by ^{249}Cf (^{15}N,4n): A. Ghiorso *et al.*, *Phys. Rev. Letters* **24**, 1498 (1970). Prepn of ^{261}105 isotope decay by spontaneous fission, $T_{1/2}$ 1.8 ±0.6 sec) by ^{243}Am (^{22}Ne,4n): G. N. Flerov *et al.*, *At. Energy (USSR)* **29**, 243 (1970); *eidem, Nucl. Phys. A* **160**, 181 (1971); *eidem, Proc. Int. Conf. Heavy Ion Phys.* **1971** pp 125-143, *C.A.* **80**, 139758y (1974). Prepn of α-emitting isotopes ^{261}105 ($T_{1/2}$ 1.7 sec) by ^{254}Es (^{16}O,4n) or by ^{250}Cf (^{15}N,4n); ^{262}105 ($T_{1/2}$ 40.0 ±10 sec, longest-lived known isotope, rel. at. mass 262.1144) by ^{254}Es(^{18}O,5n): A. Ghiorso *et al.*, *Phys. Rev.* **C4**, 1850 (1971); revised $T_{1/2}$ 34.1 ±4.6 sec for ^{262}105: C. E. Bemis, Jr. *et al.*, *Phys. Rev. Letters* **39**, 1246 (1977). Discussion of conflicting claims of discovery: Holcomb, *Science* **168**, 810 (1970); G. N. Flerov, *ibid.* **170**, 15 (1970); A. Ghiorso, *ibid.* **171**, 127 (1971). Aqueous chemistry: K. E. Gregorich *et al.*, *Radiochim. Acta* **43**, 223 (1988); M. K. Gober *et al.*, *ibid.* **57**, 77 (1992); and identification of ^{263}105 isotope ($T_{1/2}$ 27 sec, α-emitter) by ^{249}Bk(^{18}O,4n): M. Schädel *et al.*, *ibid.* 85. Reviews of history, nomenclature and properties: C. Keller, *The Chemistry of the Transuranium Elements* (Verlag Chemie, Weinheim, English Ed., 1971) pp 619-622; Silva, "Trans-Curium Elements" in *MTP Int. Rev. Sci.: Inorg. Chem., Ser. One* **vol. 8**, A. G. Maddock, Ed. (University Park Press, Baltimore, 1972) pp 71-105; R. J. Silva *The Chemistry of the Actinide Elements* **vol. 2**, J. J. Katz *et al.*, Eds. (Chapman and Hall, New York, 1986) pp 1106-1109; G. T. Hyde *et al.*, *Radiochim. Acta* **42**, 57-102 (1987); Transactinium Working Group, *Pure Appl. Chem.* **65**, 1757-1814 (1993). Review of chemistry: D. C. Hoffman, *Proc. Robert A. Welch Found. Conf. on Chem. Res., XXXIV, Fifty Years with Transuranium Elements* (Houston, Texas, 1990) pp 255-276.

3496. Dulcamara. Bittersweet; woody nightshade; scarlet berry. Dried stems of *Solanum dulcamara* L., *Solanaceae*. Native to Europe, Western Asia, Northern Africa, natural in U.S. Contains Solanoicine (about 1%), dulcamarin, dulcamaric and dulcamaretic acids.

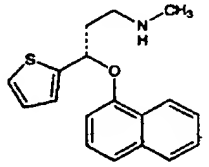
3497. Dulcin. [150-69-6] (4-Ethoxyphenyl)urea; *p*-phenolcarbamide; *p*-phenetylurea; Sucrol; Valzin. $C_9H_{12}N_2O_2$; mol wt 180.20. C 59.99%, H 6.71%, N 15.55%, O 17.76%. Prepn by treating *p*-phenetidine with phosgene and then with ammonia: Berlinerblau, *J. Prakt. Chem.* **30**, 103 (1883); from *p*-phenetidine and urea: Kurzer, *Org. Syn.* **coll. vol. IV**, 52 (1963).



Colorless needles; very sweet taste — about 250 times as sweet as sugar. mp 173-174°. Sol in 800 parts cold water. 50 parts boiling water, 25 parts alcohol.

USE: Non-nutritive sweetener.

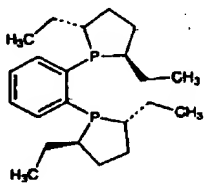
3498. Duloxetine. [116539-59-4] (γ*S*)-*N*-Methyl-γ-(1-naphthyloxy)-2-thiophenepropanamine; (+)-(*S*)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine; (+)-*N*-methyl-3-(1-naphthyloxy)-3-(2-thienyl)propanamine; LY-248686. $C_{18}H_{19}NOS$; mol wt 297.42. C 72.69%, H 6.44%, N 4.71%, O 5.38%, S 10.78%. Dual serotonin and norepinephrine reuptake inhibitor (SNRI). Prepn: D. W. Robertson *et al.*, EP 273658; US 5023269 (1988, 1991 both to Lilly); and abs config: J. Deeter *et al.*, *Tetrahedron Letters* **31**, 7101 (1990). Improved process: R. A. Berglund, US 5362886 (1994 to Lilly). Pharmacology: D. T. Wong *et al.*, *Neuropsychopharmacology* **8**, 23 (1993). Neurochemical effects *in vivo*: R. W. Fuller *et al.*, *J. Pharmacol. Exp. Ther.* **269**, 132 (1994). Determn of chiral purity: E. C. Rickard, R. J. Bopp, *J. Chromatog. A* **680**, 609 (1994). Clinical evaluation in major depressive disorder: M. Berk *et al.*, *Int. Clin. Psychopharmacol.* **12**, 137 (1997). Clinical pharmacokinetics: A. Sharma *et al.*, *J. Clin. Pharmacol.* **40**, 161 (2000).



Hydrochloride. [136434-34-9] $C_{18}H_{19}NOS.HCl$. White solid. pKa in DMF-water (66:34): 9.6.

THERAP CAT: Antidepressant.

3499. DuPHOS. Series of chiral bis(phospholane) compounds with C_2 symmetry used as rhodium complexes for catalysis. Prepn: M. J. Burk, *J. Am. Chem. Soc.* **113**, 8518 (1991); and configuration: *idem et al., ibid.* **115**, 10125 (1993). Use in asymmetric synthesis of warfarin: A. Robinson *et al, Tetrahedron Letters* **37**, 8321 (1996); hydrogenations of β-(acylamino)acrylates: G. Zhu *et al.*, *J. Org. Chem.* **64**, 6907 (1999).



(*R,R*)-Ethyl DuPHOS

(*R,R*)-Me-DuPHOS. [147253-67-6] [2*R*-[1(2′*R**,5′*R**),2α,-5β]]-1,1′-(1,2-Phenylene)bis[2,5-dimethylphospholane]. $C_{18}H_{28}P_2$; mol wt 306.36.

(*S,S*)-Me-DuPHOS. [136735-95-0] (*S,S*)-1,2-Bis(2,5-dimethylphospholano)benzene. $C_{18}H_{28}P_2$; mol wt 306.36. Colorless crystals from methanol, mp 79-81°. $[\alpha]_D^{25}$ +476± 5° (c = 1 in hexane).

(*R,R*)-Et-DuPHOS. [136705-64-1] (2*R*,2′*R*,5*R*,5′*R*)-1,1′-(1,2-Phenylene)bis[2,5-diethylphospholane]. $C_{22}H_{36}P_2$; mol wt 362.47. Colorless oil. $[\alpha]_D^{25}$ −265° (c = 1 in hexane). $bp_{0.045\ mm}$ 138-145°.

USE: Catalyst for asymmetric hydrogenations.

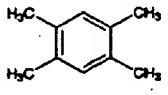
3500. Durapatite. [1306-06-5] Hydroxylapatite; calcium phosphate hydroxide; calcium orthophosphate basic; hydroxyapatite; Alveograf; Ossopan; Periograf. $3Ca_3(PO_4)_2.Ca(OH)_2$ or $Ca_{10}(PO_4)_6(OH)_2$. Also considered as pentacalcium monohydroxyorthophosphate $Ca_5(OH)(PO_4)_3$. Calcd as $Ca_{10}H_2O_{26}P_6$: Ca 39.89%, H 0.20%, O 41.41%, P 18.50%. Occurs as a mineral in phosphate rock. Constitutes the mineral portion of bone. Prepn from $Ca(NO_3)_2$ and KH_2PO_4: Warington, *J. Chem. Soc.* **26**, 983 (1873); Rathje, *Ber.* **74**, 342 (1941); Hayek in *Handbook of Preparative Inorganic Chemistry*, G. Brauer, Ed. (Academic Press, 2nd ed., 1963) p 545; from calcium phosphate, dibasic: Perloff, Posner, *Inorg. Syn.* **6**, 16 (1960); from $Ca(NO_3)_2.4H_2O$ and $(NH_4)_3PO_4$ plus NH_4OH: Hayek, Newesely, *ibid.* **7**, 63 (1963). Formation and structure of synthetic bone hydroxyapatites: A. S. Posner *et al., Prog. Cryst. Growth Charact.* **3**, 3 (1980).

Hexagonal needles arranged in rosettes. Dec above 1100°. Practically insol in water, even when freshly prepd. Crystallographic data: a_0 9.425; C_0 6.935; C_0/a_0 0.736.

USE: Prosthetic aid (artificial bone and teeth).

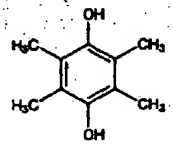
THERAP CAT: Calcium supplement; phosphorus supplement.

3501. Durene. [95-93-2] 1,2,4,5-Tetramethylbenzene; Durol. $C_{10}H_{14}$; mol wt 134.22. C 89.49%, H 10.51%. Occurs in coal tar. Usually prepd from xylene and methyl chloride in the presence of $AlCl_3$: Smith, *Org. Syn.* vol. 10, 32 (1930); *cf.* Smith, Dobrovolny, *J. Am. Chem. Soc.* 48, 1413 (1926).



Scales with camphor-like odor from alcohol. d_4^{41} 0.84. mp 80°. bp 191-193°. Sublimes and is volatile with steam. Insol in water; freely sol in alcohol, ether, benzene.

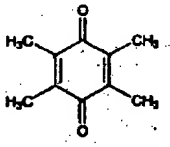
3502. Durohydroquinone. [527-18-4] 2,3,5,6-Tetramethyl-1,4-benzenediol; tetramethyl-*p*-hydroquinone; dihydroxydurene. $C_{10}H_{14}O_2$; mol wt 166.22. C 72.26%, H 8.49%, O 19.25%. For prepn *see* refs under Duroquinone.



Needles from alcohol. mp 233°. Begins to sinter at 220°. Sparingly sol in ether. Treatment with ferric chloride yields duroquinone.

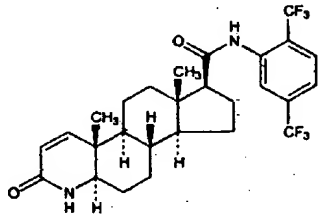
Diacetyldurohydroquinone. Needles from alc, mp 207°.

3503. Duroquinone. [527-17-3] 2,3,5,6-Tetramethyl-2,5-cyclohexadiene-1,4-dione; tetramethyl-*p*-benzoquinone. $C_{10}H_{12}O_2$; mol wt 164.20. C 73.15%, H 7.37%, O 19.49%. Prepn by reduction of dinitrodurene: Smith, *Org. Syn.* vol. 10, 40 (1930); Smith, Dobrovolny, *J. Am. Chem. Soc.* 48, 1420 (1926); by condensation of 2,3-diketopentane with itself in presence of alkalies: von Pechmann, *Ber.* 21, 1420 (1888); by the action of alkalies on 3,3-dichloropentan-2-one: Faworsky, *J. Prakt. Chem.* [2] 51, 538 (1895).



Yellow needles from alc, mp 111-112°. Sublimes. Volatile with steam. Insol in water; sol in alcohol, benzene, ether, hot petr ether.

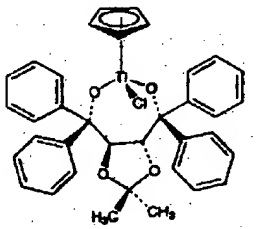
3504. Dutasteride. [164656-23-9] (4a*R*,4b*S*,6a*S*,7*S*,9a*S*,9b*S*,11a*R*)-*N*-[2,5-Bis(trifluoromethyl)phenyl]-2,4a,4b,5,6,6a,7,8,9,9a,9b,10,11,11a-tetradecahydro-4a,6a-dimethyl-2-oxo-1*H*-indeno[5,4-*f*]quinoline-7-carboxamide; 17β-*N*-[2,5-Bis(trifluoromethyl)phenyl]carbamoyl-4-aza-5α-androst-1-en-3-one; GG-745; GI-198745. $C_{27}H_{30}F_6N_2O_2$; mol wt 528.53. C 61.36%, H 5.72%, F 21.57%, N 5.30%, O 6.05%. Inhibits both isozymes of 5α-reductase; structurally related to finasteride, *qv*. Prepn: K. W. Batchelor, S. V. Frye, WO 95 07927 (1995 to Glaxo). Structure-activity study: R. K. Bakshi *et al.*, *J. Med. Chem.* 38, 3189 (1995). Clinical pharmacokinetics: P. O. Gisleskog *et al.*, *Brit. J. Clin. Pharmacol.* 47, 53 (1999). Review of discovery and development: S. V. Frye *et al.*, *Pharm. Biotechnol.* 11, 393-422 (1998).



White crystalline solid, mp 245-245.5°.

THERAP CAT: In treatment of benign prostatic hyperplasia.

3505. Duthaler-Hafner Reagent. [132068-98-5] Chloro(η⁵-2,4-cyclopentadien-1-yl)[(4*R*,5*R*)-2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2−)-κ*O*⁴,κ*O*⁵]-titanium. $C_{36}H_{33}ClO_4Ti$; mol wt 612.98. C 70.54%, H 5.43%, Cl 5.78%, O 10.44%, Ti 7.81%. Enantioselective allyl-transfer reagent. Prepn: R. O. Duthaler *et al.*, *Pure Appl. Chem.* 62, 631 (1990). As reagent in prepn of titanium transmetallation complexes: A. Hafner *et al.*, *J. Am. Chem. Soc.* 114, 2321 (1992). Use in aldol reactions: R. C. Cambie *et al.*, *Aust. J. Chem.* 46, 583 (1993); in asymmetric allylation: A. Fürstner, K. Langemann, *J. Am. Chem. Soc.* 119, 9130 (1997). Review of prepn, structure and use: R. O. Duthaler *et al.*, in *Proc. 3rd Symp. Org. Synth. Organomet. 1990*, K. H. Doetz, R. W. Hoffmann Eds. (Vieweg, Braunschweig, Germany, 1991) pp 285-309.

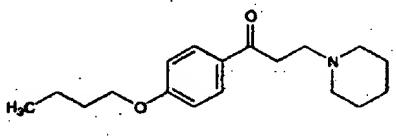


mp 209-213°. $[\alpha]_D^{20}$ −246° (c = 1 in $CHCl_3$). Moisture sensitive, store under nitrogen. *Corrosive.*

(*S,S*)-Form. [140462-73-3] mp 209-213°. $[\alpha]_D^{20}$ +246° (c = 1 in $CHCl_3$). Moisture sensitive, store under nitrogen. *Corrosive.*

USE: Transmetallation of allyl-Grignard or allyl-Li compounds.

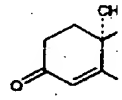
3506. Dyclonine. [586-60-7] 1-(4-Butoxyphenyl)-3-(1-piperidinyl)-1-propanone; 3-piperidino-4'-butoxypropiophenone; β-piperidinoethyl-4-butoxyphenyl ketone; 4-butoxy-β-piperidinopropiophenone; 4-*n*-butoxy-β-(1-piperidyl)propiophenone; 4-butoxyphenyl piperidineethyl ketone; 2-(1-piperidyl)-ethyl *p*-butoxyphenyl ketone. $C_{18}H_{27}NO_2$; mol wt 289.41. C 74.70%, H 9.40%, N 4.84%, O 11.06%. Prepd from *p*-butoxyacetophenone by condensation with formaldehyde and piperidine hydrochloride: Pufft, *Chem. Tech. (Berlin)* 4, 241 (1952); *C.A.* 47, 10531 (1953). *Compare* Fallcain.



Hydrochloride. [536-43-6] Dyclone; Tanaclone. $C_{18}H_{27}NO_2$.HCl; mol wt 325.88. Crystals, mp 175-176°. Sol in water, alc, acetone. Phenol coefficient 3.6.

THERAP CAT: Anesthetic (local).

3507. Dydrogesterone diene-3,20-dione; 10α-preg dro-*retro*-progesterone; 10α- ton: Gynorest; Prodel; Retr 80.73%, H 9.03%, O 10.24% *Trav. Chim.* 79, 771 (1960); (1961).



Crystals from acetone + he (chloroform). uv max: 286.5 THERAP CAT: Progestogen

3508. Dymanthine. [1 decanamine; *N,N*-dimethylo $H_{41}N$; mol wt 297.56. C 80. $(CH_2)_{17}N(CH_3)_2$. Prepd fro hyde: Reck *et al.*, *J. Org. C* mp 22.89°.

Hydrochloride. [1613-17 mesan. $C_{20}H_{42}N.HCl$; mol w THERAP CAT: Anthelmintic THERAP CAT (VET): Antheli

3509. Dynamin. GTPas essential role in membrane bu ious isoforms which are tiss Homotetramer which self-ass form collars at the fission po H. S. Shpetner, R. B. Vallee, mechanism of membrane fiss 77, 604 (1999). Review of fu ratia *et al.*, *Proc. Nat. Acad.* functions: M. A. McNiven *et* 120 (2000). Review of structu *Curr. Opinion Struct. Biol.* 9, tional diversity and related d der Bliek, *Trends. Cell Biol.* 9

3510. Dynel. Staple fibe ride and 40% acrylonitrile wet as much as 1300% and then a Stout, *Introduction to Textiles* pp 198-201; R. W. Moncrieff, New York, 1963) pp 411-420 in *Encyclopedia of Polymer Sc* M. Bikales, Ed. (Interscience,

Light cream fiber which can cific gravity 1.31. Tenacity r Elongation is 30-40%; hygros conditions. Has extremely goo is the best solvent; cyclohexan have some solvent action. Ace illine, ethylene dichloride, and or swell dynel. Resistant to beetles, and to mildew and fun the flame is removed it is self-e and non-felting and non-shrinl delusters dynel. Must be ironed a dry cotton cover over the fabri pleats. Can be dyed readily an tant to perspiration and to salt-

USE: In apparel and house coats; chemically resistant clot hair; the hair can be washed, co redyed.

[redacted]

GRANT & HACKH'S

CHEMICAL DICTIONARY

[American, International, European and British Usage]

Containing the Words Generally Used in Chemistry, and Many of the Terms Used in the Related Sciences of Physics, Medicine, Engineering, Biology, Pharmacy, Astrophysics, Agriculture, Mineralogy, etc.

Based on Recent Scientific Literature

FIFTH EDITION
Completely Revised and Edited by

ROGER GRANT

M.A., D. de l'U., Ph.D., C. Chem., M.R.S.C. *Consultant*

CLAIRE GRANT

M.B., B.S., M.R.C.P.E. *Medical Practitioner*

McGRAW-HILL, INC.

New York St. Louis San Francisco Auckland Bogotá
Caracas Lisbon London Madrid Mexico Milan
Montreal New Delhi Paris San Juan São Paulo
Singapore Sydney Tokyo Toronto

ketone of salicylic acid and resorcinol, 2,2'4-trihydroxybenzophenone. Colorless leaflets, soluble in water.

salicylyloyl The salicyloyl* radical.

salify To form a salt.

saligenin (1) Salicyl alcohol*. (2) Salicin. **homo ~** Salicyl alcohol*.

saligenol Salicyl alcohol*.

salimeter A hydrometer to determine the density of salt solutions. Cf. *salinimeter.*

saline (1) Saltlike. (2) A salt spring or well. (3) Describing the taste of common salt. (4) Containing sodium chloride. **physiologically normal ~** A sterilized 0.9% solution of common salt in water. Isotonic with blood and tissue fluids. Chemically normal is 5.85%.

salines Salt springs; salt lands.

salinigrin $C_{13}H_{16}O_7$ = 284.3. Piceoside. The β-D-glucoside of 4'-hydroxyacetophenone, m.195. From the bark of *Salix nigra*, willow.

salinimeter A hydrometer for determining the salt content of brine or seawater. Cf. *salimeter.*

salinity (1) A comparative indication of the concentration of salts in natural waters. (2) The number of grams of salt in 1 kg seawater, when bromides and iodides are converted to chlorides, the carbonates to oxides, organic matter destroyed, and the mass heated at 450°C for 72 hours. $S = 0.03 + 1.805$ Cl content.

salinometer An instrument which uses the electrical conductivity of water to control salt content. Cf. *salinimeter.*

saliretin $C_{14}H_{14}O_3$ = 230.3. A yellow resin from salicin.

saliseparin Smilacin.

salit Bornyl salicylate*.

saliter, salitre Sodium nitrate*.

salithymol $C_6H_4(OH)COOC_{10}H_{13}$ = 270.3. Thymol salicylate. Colorless crystals, insoluble in water; an antiseptic.

saliva The alkaline secretion of the salivary glands; contains digestive enzymes (α-amylase), salts (potassium thiocyanate), proteins (albumin). The composition depends on the diet and can cause tartar formation on teeth. Cf. *sputum.*

Salix The willows (Salicaceae) whose bark yields salicin. **S. alba** The European or white willow. **S. fragilis** The brittle willow, snap willow. Its bark is an astringent and febrifuge. **S. nigra** The pussy willow (American, black, or swamp willow). Its bark is an antipyretic and sedative.

Salkowski's solution A solution of phosphotungstic acid; used to test for albumose in urine.

salmak Ammonium chloride.

salmiac Ammonium chloride.

salmine $C_{30}H_{57}O_6N_{14}$ = 709.9. A protamine from salmon spermatozoa.

salmonellosis Food poisoning, which can be fatal, due to organisms mainly of the *Salmonella typhimurium* type, especially from poultry.

salol Phenylsalicylate*. **nitro ~** See *nitrosalol.*

salseparin Smilacin.

salseparisin Parillin.

salsoline $C_{11}H_{15}NO_2$ = 193.2. (*S*)-1,2,3,4-Tetrahydro-7-methoxy-1-methyl-6-isoquinolinol. m.220. An alkaloid from *Salsola Richteri* (Cactaceae). Cf. *carnegine.*

salt (1) See *salts.* (2) Common s., halite, or sodium chloride. **air ~** See *air salt.* **baker's ~** Ammonium carbonate. **bay ~** Sodium chloride from seawater. **bitter ~** Magnesium sulfate*. **Carlsbad ~** A mixture of sodium and potassium sulfates, sodium hydrogencarbonate, and sodium chloride. **common ~** Sodium chloride*. **diuretic ~** Potassium acetate*. **Epsom ~** Magnesium sulfate*. **Everitt's ~** Potassium hexacyanoferrate(III)*. **Glauber ~** Sodium sulfate*. **green ~** Uranium tetrafluoride*. **Homberg's ~** Boric acid. **iodized ~** Sodium chloride, with a trace of iodide, for table use. **melting ~** A s., e.g., the carbonate and phosphate of sodium, melted with cheese during processing to improve emulsification and texture. **microcosmic ~** See *microcosmic salt.* **Mohr ~** See *Mohr salt.* **Monsel's ~** Ferric subsulfate. **pepetic ~** A mixture of sodium chloride and pepsin. **phosphor ~** Microcosmic s. **Plimmer's ~** Antimony sodium tartrate. **Preston's ~** An aromatized ammonium carbonate; a smelling s. **rochelle ~** Potassium sodium tartrate*. **rock ~** Sodium thioantimonate*. **sea ~** Sodium chloride from seawater. **Seignette's ~** Potassium sodium tartrate*. **solar ~** S. produced by evaporation of seawater by the sun. **Sorrel ~** Potassium hydrogenoxalate*. **spirits of ~** Commercial hydrochloric acid. **Stassfurt ~** Stassfurt salts. **sweet ~** Sodium chlorite*. **table ~** Sodium chloride*.

s. of amber Succinic acid*. **s. cake** (1) Impure sodium sulfate, e.g., as a by-product of the Leblanc soda process, or from natural Glauber salt. (2) A synthetic s. cake made by fusing sulfur and sodium carbonate together in the correct proportions. **s. deposits** Saline residues. The accumulation of salts from the evaporation of natural waters, as at Strassfurt, q.v. *(Stassfurt salts),* and in the desert. Chiefly carbonates, chlorides, sulfates, and borates of sodium, potassium, calcium, and magnesium. **s. glaze** See *salt glaze* under *glaze.* **s. hydrates** The solid phases, salt and water; hence any crystal with one or more molecules of water of crystallization. **s. ice** Frozen brine, m. −21. **s. of lemon** Potassium hydrogenoxalate*. **s. peter** See *saltpeter.* **s. of phosphorus** Ammonium sodium hydrogenphosphate. **s. solution** Saline solution. **s. of sorrel** Potassium hydrogenoxalate*. **s. of tartar** Potassium hydrogentartrate*. **s. of tin** Stannous chloride. **s. of vitriol** Zinc sulfate*. **s. of wormwood** Potassium carbonate*.

salting Treating with salt. **s. in** The mutual increase in the solubilities of an electrolyte and an organic compound added to the same solvent. **s. out** Aiding liquid–liquid extraction by addition of an electrolyte. Separation of a substance from its solution by adding soluble salts; as, precipitation of proteins by salts.

saltpeter, saltpetre Potassium nitrate*. **Chile ~** Sodium nitrate*. **German ~** Ammonium nitrate*. **Norge ~, Norway ~** Calcium nitrate*.

salts Substances produced from the reaction between acids and bases; a compound of a metal (positive) and nonmetal (negative) radical: M·OH (base) + HX (acid = MX (salt) + H_2O (water). **acid ~** S. containing unreplaced H atoms from the acid; as, $NaHSO_4$. **acidic ~** S. having an acid reaction. **alkaline ~** S. having a basic reaction. **amphoteric ~** S. having both acid and basic reactions. **basic ~** S. containing unreplaced hydroxyl radicals of the base; as $Bi(OH)Cl_2$. **binary ~** Compounds of 2 bases and one acid radical; as, $NaKSO_4$. **complex ~** S. made up of more than one simple acid or metallic radical, but which ionize in solution into only 2 types of ions. Thus potassium hexacyanoferrate(II): $K_4Fe(CN)_6 = 4K^+ + Fe(CN)_6^{4-}$. Cf. *Werner's theory.* **double ~** A molecular combination of 2 s.; as, alums: $M_2SO_4 \cdot M_2(SO_4)_3 \cdot 24H_2O$. Cf. complex *salts.* **ethereal ~** An ester. **mixed ~** S. of 2 or more metals; as, $NaKSO_4$. **neutral ~** S. having a neutral reaction, as potassium chloride. **normal ~** Compounds of a base and acid that have completely neutralized each other. **oxy ~** Compounds of a base with an oxyacid radical. **triple ~** S. containing 3 metals; as, triple chloride.

salufer Sodium hexafluorosilicate*.

salumin Aluminum salicylate.

Saluric Trademark for chlorothiazide.

salvarsan /

salve See *o*

salvia Sage (Labiatae). I principles; a

salvianin N

salviol C_{20} m.108. From

sama conditi complete eq gravitational

samandaridi *Salamandra salamandaria*

samandarin skin secretio

samaric Sa samarium. crystals, solu crystals, m.6 = 364.8. C hydroxide S water. s. n soluble in w Colorless cry $8H_2O$ = 733 water. s. su

samarium* at. no. 62, d d.7.7, m.108 s.(2+)*, sam and pink salt 348.7. White

samarous S samarium. m.740; solub $SmSO_4$ = 24

samarskite cerium, and

sambucinin sambucus.

sambucus E species, elde

sambunigrin glucopyranos leaves of *Sam* (−)-mandelo

samin $C_{13}H$ sesamolin. C

samneh Ren

samphire C (Umbelliferae

sample A re systematicall analysis. See

sampler Riff aggregates of device for cor drawing atmo matter for sub

sand Particle ~ Ilmenite. to polish plati Ti 5%. oil ~ with hot acids extraction. t

s. bath A h